REMARKS

I. Examiner's Grounds for Rejection

In the Office Action, the examiner variously rejected pending claims 1-58, 61-79 and 81-109 under 35 USC §112, second paragraph, for asserted indefiniteness, and under 35 USC §112, first paragraph, for assertedly lacking enablement and written description in the specification. The claims were also variously rejected under 35 U.S.C. §103(a) as follows: claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79, and 109 as obvious over Shan et al., *J Immunol* 162:6589-95, 1999 (hereinafter "Shan") in view of Pluckthun, US Patent 6,815,540 (hereinafter "Pluckthun"); claims 1, 56, 65, 70-72 under 103(a) as obvious over Shan and Pluckthun in view of Bodmer, US Patent 5,677,425 (hereinafter "Bodmer"); claims 1, 63, 66, and 82 as obvious over of Shan and Pluckthun further in view of Bodmer and Morrison, US Patent 6,284,536 (hereinafter "Morrison"); and claims 1, 64, 67, 73-75, 77 and 81 as obvious over Shan and Pluckthun further in view of Roux et al., *J Immunol* 161:4083-90, 1998 (hereinafter "Roux").

Applicants respectfully request reconsideration in light of the amendments and response filed herein.

II. Support for the Amendment to the Claims

Support for the amendment to the claims is found throughout the specification. Support for claims 1, 76, 77, 84-92, 94, 97-103, 105-109 and new claims 111 and 112 is found, for example, at page 106, line 16, to page 107, line 14, which describe that the connecting region may be derived from a wild-type immunoglobulin hinge peptide and the hinge may be described in terms of the number and order of the cysteine residues in the hinge peptide. Page 76, line 24 to page 80, line 10, describes hinge sequences, including CXC and XXC hinges (e.g., CSC and SSC), exemplified in the specification, including hinges wherein the proline residue is optionally replaced by serine. Claim 110 has been amended for clarity.

The amendments include no new matter.

III. The Rejection of Claim 13 and 110 under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

The examiner maintained the rejection of claim 13 for the recitation of the term "des-leucine." Cancellation of claim 13 renders the objection moot.

The examiner also objected to claim 110 as assertedly indefinite for the recitation of the name of the polypeptide construct and reference to the polypeptide's amino acid sequence. Claim 110 has been amended to clarify that the amino acid sequence of the named construct is represented in SEQ ID NO: 329.

IV. The Rejection of Claims 1-28, 31-58, 61-79, 81, 82 and 109 under 35 U.S.C. §112, First Paragraph-Enablement, Should Be Withdrawn

The examiner maintains the rejection of claims 1-28, 31-58, 61-79, 81, 82 and 109 under 35 U.S.C. §112, first paragraph, as assertedly lacking enablement for a binding-domain Ig fusion protein having specificity for any antigen or which comprises any amino acid substitution or deletion in position 9, 10, 11, 12, 108, 110, 112 in the VH region or amino acids 12, 80, 81, 83, 105, 106, and 107 in the VL region. The examiner asserts that the proposed amino acid changes could not be made predictably by one of ordinary skill such that a polypeptide construct having an amino acid change could be predicted to maintain the binding of the parent polypeptide, and asserts that the specification provides insufficient guidance to make the polypeptides recited in the claims.

The examiner acknowledged previously that the application does enable substitutions at VH amino acids 9, 10, 11, 123, 108, 110 and 112 or amino acids 12, 80, 81, 83, 105, 106, and 107 in the VL region for the amino acids listed in the specification. However, the examiner contends that Applicants have not taught which modifications could be predictably made and which choice is likely to be successful. The claims as amended are directed to a polypeptide having a substitution at position 11 and one other substitution in specified VH or VL residues. Thus, the number of amino acid substitutions in any one polypeptide can be made by a person of skill in the art using routine experimentation.

As the examiner cited in the previous action, the "*Wands* factors," are often cited as the guideline for determining enablement. *Wands* involved an invention requiring screening of large numbers of hybridomas to identify specific hybridomas within the claim limitations. The court held that the claims were enabled based on the guidance to make and screen the hybridomas and limited working examples provided in the specification. *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988). The Court in *Wands* considered that the inventor's disclosure provides considerable direction and guidance on how to practice the invention and presents working examples, and does not hold that a specific number of

working examples is required. *Id* at 740. This fact, coupled with the high level of skill in the art, renders the invention enabled in the courts' opinion. *Id.* The court held that the need for routine screening to practice variations of the invention does not negate enablement, and also held that routine screening, even of a large number of candidates, is not undue experimentation.

As stated previously, paragraph 346 of the PGPUB of the specification describes several publications which describe methods of engineering framework regions and CDR in the antibody variable region, and methods to achieve functional antibodies after modification of these regions, teaching that areas that are in contact with other domains of the antibody (e.g. CH1 or VL if a heavy chain variable region) may be altered in single chain proteins of the present invention not having these binding needs. Additionally, WO92/01787 and WO98/02462 describe residues of the variable regions in which amino acid substitutions may be made. Further, the specification teaches methods for determining whether the constructs having mutations in any one of these amino acid residues are functional, such as assessing binding to cells expressing the antigen of interest (see Example 2), and Examples 20, 34, 35, 38, 41 and 42 demonstrate that constructs of the invention, which are specific to various target molecules such as CD20 and CD37, bind their respective target antigen and exhibit effector function. The methods disclosed may be used to assess binding and effector function of any molecule of interest. As such, the current disclosure teaches methods for making the sequence alterations, methods for screening the effector function of the molecules which are routine in the art, and provides working examples of constructs of the invention. One of ordinary skill can readily make and use the invention with some experimentation but without undue burden using routine techniques, similar to the facts of the case in *Wands*.

Moreover, the Examiner provides twelve different pre-filing references, and one post filing reference that indicates that antibody engineering was well-known to one of ordinary skill in the art. For example, McCallum, Pascalis, Casset, Vajdos, Chen and Wu disclose methods for determining the exact antigen binding site of an antibody, and teach that many of the antigen binding contact residues are in the CDR of the Ig variable region. These references also identify framework region residues that are important in antibody structure and antigen contact in some manner. In addition, the authors of the references cited by the examiner analyze binding using such techniques as alanine scanning mutagenesis and other

mutagenesis techniques, which generates constructs having mutations at every amino acid in the variable region, or at a minimum in the CDR, thus resulting in tens of thousands of constructs that are screened using routine technology. The art is replete with evidence that one of ordinary skill can readily make thousands of variable region variants, assess the variants for antigen binding structure and identify residues within the variable region that may be substituted without significant alteration of antibody activity. Thus, this amount of experimentation is not undue as asserted by the examiner, but is routine experimentation.

Further, Brummell, Kobayashi, Burks and Jang demonstrate that one of ordinary skill can readily mutate CDR residues and determine binding affinity of the antibody. For example, Burks discloses random mutagenesis of a scFv and further screening of 114 candidate variants for antigen affinity, demonstrating that generation of multiple variants and screening of their binding activity is routine and does not place an undue burden on one of ordinary skill.

Additionally, the majority of the art cited by the examiner describes mutation of variable regions in the CDR which are highly involved in antigen binding. The amino acid substitutions recited in the claims are not within the art recognized heavy or light chain CDR (see MacCallum et al., Table 3, which sets out the residues of the putative heavy and light chain CDR). Thus the recited changes are not within important antigen binding contacts that would be more likely to interrupt antigen binding and effector function as asserted by the examiner, and result in more predictable modification than those in the art cited by the examiner.

Thus, in view of the decision in *Wands* that routine screening is not undue experimentation, the examiner's assertion that the sheer number of constructs to be screened to find a polypeptide within the scope of the present invention is undue is incorrect. The evidence in the art demonstrates that a substantial number of variable region amino acid variants are readily screened using well-known techniques and one of ordinary skill can easily generate and screen numerous variants without undue experimentation.

Moreover, the claims as amended are directed to changes in specific framework amino acid residues in the VH or VL region and not to <u>any</u> amino acid change at <u>any</u> position in the variable region as the examiner appears to suggest. A worker of ordinary

skill does not need to try to imagine which amino acid residues to change, since the claims specify that one of a limited number of amino acid residues may be changed. As such, the change in the amino acid is predictable as there are a limited number of choices to which a single amino acid can be altered. Moreover, the residues in an immunoglobulin variable region are highly conserved such that the worker of ordinary skill can readily determine which residues in a variable region are within domains that may be altered. See e.g., Kabat et al. ((1991) Sequences of Proteins of Immunological Interest , 5th Ed. , Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD) which describes the conserved residues in the framework and CDR regions. As such, variations at the amino acid residues recited in the claims may be made in antibody variable regions without undue experimentation.

Given the high level of skill in the art of recombinant protein engineering, coupled with the teaching in the specification of methods to modify antibody variable regions, methods of screening for binding affinity, and working examples of the constructs of interest having a variable region with at least one amino acid change, one of ordinary skill would be able to make and use a construct of the invention comprising a mutation in either a heavy chain or a light chain variable region in an claimed fusion protein without undue experimentation. Therefore, the rejection of claims 1-28, 31-58, 61-79 and 81, 82 and 109 as lacking enablement under 35 USC §112, first paragraph, should be withdrawn.

V. The Rejection of Claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79 and 109 under 35 U.S.C. §103(a) Should Be Withdrawn

The examiner maintains the rejection of claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79 and 109 under 35 U.S.C. §103(a) as allegedly obvious over Shan and Pluckthun. The examiner contends that Shan discloses modification of monovalent and bivalent scFv and asserts that it would be obvious for one of ordinary skill in the art to take a protein construct of Shan and modify the protein according to the teachings of Pluckthun.

The rejected claims are dependent from either claims 1 or 77 which are directed to a single chain protein having a binding domain comprising a heavy chain variable region with a modification at position 11 in the heavy chain variable region and having a

hinge peptide which is derived from a wild-type IgG1 hinge and having either the second cysteine replaced by amino acid substitution, or the first and second cysteines replaced by amino acid substitution.

To establish a *prima facie* case of obviousness, the Examiner must show that all the elements of the claim are taught or suggested in the prior art (MPEP 2143.03 and Federal Register Examination Guidelines for Determining Obviousness, Section III.A.1, Fed Reg., Vol 72, No. 195, 2007), and if all claim elements are described in the art, the combination of elements *must yield predictable results* to render a clamed invention obvious. Further, it should be demonstrated that there was some teaching, suggestion or motivation in the prior art or the knowledge generally available to an ordinary artisan to combine the references, and there was a reasonable expectation that such a combination would successfully result in the claimed invention (MPEP 2142 and Federal Register Examination Guidelines for Determining Obviousness, Section III.G, Fed Reg., Vol 72, No. 195, 2007). The examiner must provide "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir 2006)).

The examiner has not established a *prima facie* case of obviousness because not all of the claim elements are present in the cited art. Neither Pluckthun nor Shan, taken alone or in combination, disclose or suggest a polypeptide having the structure of the presently claimed polypeptides, having a VH11 modification and having a hinge region with either a CXC or XXC cysteine sequence. Shan does not disclose or suggest a construct having a change in the heavy chain variable region, especially not a change at position 11, and neither discloses nor suggests altering the hinge region to have a CXC or XXC hinge sequence. Pluckthun does not remedy the deficiencies of Shan. Pluckthun does not disclose or suggest a construct having the structure of the present invention and having a change in the heavy chain variable region, and neither discloses nor suggests altering the immunoglobulin hinge region to have a CXC or XXC hinge sequence.

As stated above, Shan and Pluckthun fail to disclose or suggest all the elements of the claimed invention. Therefore, a prima facie case of obviousness has not been established. Accordingly, Applicants respectfully request that the rejection of claims 1-12,

14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 66, 65, 68, 69, 71, 72, 76-79 and 109 under §103(a) be withdrawn..

VI. The Rejection of Claims 1, 56, 65 and 70-72 under 35 U.S.C. §103(a) Should Be Withdrawn

The examiner maintained the rejection of claims 1, 56, 65, and 70-72 under 35 U.S.C. §103(a) as allegedly obvious over Shan and Pluckthun further in view of Bodmer.

The claims are directed to a single chain protein having a binding domain comprising a heavy chain variable region with a modification at residue 11 and specific hinge regions having either a CXC or XXC hinge seqeunce, further wherein the Ig region is humanized (claim 56), wherein the connecting region comprises a human IgG1, IgG2, IgG3 or IgG4 hinge region having at least one cysteine residue (claim 65) or wherein the connecting region has one cysteine residue, comprises no more than one cysteine residue or wherein the connecting region is altered so that said protein has a reduced ability to dimerize (claims 70-72).

As an initial matter, Applicants submit that the rejection of claims 65 and 70 have been rendered moot since these claims have been canceled without prejudice.

Shan and Pluckthun have been described above. Bodmer describes a tetrameric antibody construct comprising variable regions, a hinge, CH1, CH2 and CH3 regions, wherein the altered antibodies have a reduced number of cysteine residues in the hinge region. Bodmer neither discloses nor suggests a construct having the structure of the claimed constructs, nor describes modification of position 11 of the heavy chain variable region or modification of the hinge connecting region as set out in the claims.

As stated above, the combination of Shan and Pluckthun does not provide all the elements of the claimed invention and Bodmer does not remedy this deficiency, therefore all the elements of the claims are not disclosed in the cited art. Thus, the Examiner has failed to establish a prima facie case of obviousness for any of the rejected claims and the rejection of claims 1, 56, 71 and 72 under 35 U.S.C. §103(a) should be withdrawn.

VII. The Rejection of Claims 1, 63, 66 and 82 under 35 U.S.C. §103(a) Should Be Withdrawn

The examiner maintained the rejection of claims 1, 63, 66, and 82 under 35 U.S.C. §103(a) as allegedly obvious over Shan and Pluckthun further in view of Bodmer and Morrison.

The claims are directed to single chain proteins of the invention comprising a VH domain having a modification at position 11 having a hinge connecting region derived from an IgG1 hinge and having a CXC or XXC cysteine sequence. Amendment to the claims renders the present rejection moot, and the rejection of the claims as obvious over Shan and Pluckthun in view of Bodmer, further in view of Morrison, should be withdrawn.

VIII. The Rejection of Claims 1, 64, 67, 73-75, 77 and 81 under 35 U.S.C. §103(a) Should Be Withdrawn

The examiner maintained the rejection of claims 1, 64, 67, 73-75, 77 and 81 under 35 U.S.C. §103(a) as allegedly obvious over Shan and Pluckthun further in view of Roux.

Shan and Pluckthun have been described above. Roux describes antibodies having IgE and IgG1 hinge regions and describes generating hinge regions having proline substitutions at the cysteine residues. Roux neither discloses nor suggests modification of the variable regions nor discloses a single chain protein having the hinge region structure of the claimed polypeptides.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness for any of the rejected claims and the rejection of claims 1, 64, 67, 73-75, 77 and 81 under 35 U.S.C. §103(a) as obvious over Shan and Pluckthun further in view of Roux should be withdrawn.

IX. Conclusion

Applicants submit that the application is in condition for allowance and request notification of the same.

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Respectfully submitted,

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